Published in final edited form as:

Expert Rev Respir Med. 2009 ; 3(2): 187–196. doi:10.1586/ERS.09.5.

Therapies for scleroderma-related pulmonary arterial hypertension

Paul M Hassoun

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD 21224, USA, Tel.: +1 410 614 5158, Fax: +1 443 287 3349, phassoun@jhmi.edu

Abstract

Pulmonary arterial hypertension (PAH), a common complication of systemic sclerosis, carries a very severe prognosis and is one of the leading causes of death in patients who suffer from it. Indeed, response to modern medical therapy has been disappointing in scleroderma-related PAH compared with other forms of PAH from the WHO group 1 classification of diseases, despite similar histological changes involving the pulmonary vasculature. This review discusses specific features of scleroderma-related PAH, currently available and US FDA-approved therapy for this syndrome, as well as potential future therapeutic developments based on newly acquired knowledge of this disorder.

Keywords

endothelin receptor antagonist; phosphodiesterase inhibitor; prostaglandin; pulmonary arterial hypertension; scleroderma; therapy

Pulmonary hypertension, defined as a mean pulmonary arterial pressure above 25 mmHg, is a cause of significant morbidity and mortality [1–3]. Pulmonary arterial hypertension (PAH; defined as mean pulmonary arterial pressure greater than 25 mmHg, with pulmonary capillary wedge pressure equal to or less than 15 mm Hg and pulmonary vascular resistance greater than 3 wood units) includes a heterogeneous group of clinical entities with characteristic pathological changes that has been subcategorized as idiopathic PAH (IPAH; formerly known as primary pulmonary hypertension), familial PAH, pulmonary hypertension associated with connective tissue disease (CTD; e.g., systemic sclerosis), portal hypertension, congenital systemic-to-pulmonary shunts, HIV infection, drugs and toxins, and other disorders, such as hemoglobinopathies, including sickle-cell disease, Gaucher's disease and hereditary hemorrhagic telangiectasia [4]. The present review focuses on therapy of scleroderma-related PAH.

Pulmonary arterial hypertension is characterized by increased pulmonary vascular resistance due to remodeling and occlusion of the pulmonary arterioles. Left untreated, PAH leads irretrievably to right ventricular (RV) hypertrophy, pressure overload and dilation, resulting in death, generally from RV failure, within 2–3 years of the initial diagnosis [1]. It has been increasingly appreciated that the integrity of RV function, rather than the degree of pulmonary vascular injury, is the major determinant of symptoms and mortality in patients with PAH [1, 5]. In fact, RV dysfunction at time of presentation, as reflected by an elevation in right atrial pressure, the presence of pericardial effusion or depressed cardiac output, is by far the best prognosticator of death [1].

Until recently, there was no effective therapy for severe PAH (particularly IPAH), a disease with a median survival estimated to be approximately 2.5 years following the first clinical symptoms [1]. However, in the past two decades, novel therapies have been developed based on the concept that endothelial cell dysfunction and an imbalance between endothelial-derived vasoactive substances were central to the pathogenesis of severe PAH [6]. Thus, a focus on the pulmonary vascular endothelium and its role in regulating smooth muscle cell tone and proliferation has helped unravel some of the mechanisms involved in the pathogenesis of PAH, and eventually led to the use of various agents that act upon three essential biological pathways – the endothelin, nitric oxide/cGMP and prostacyclin pathways [7]. Aside from alleviating symptoms, therapy aims to improve functional activity and quality of life, and prolong survival, all of which have been partially achieved with currently available therapies, but mostly in patients with IPAH [7]. Indeed, it has become clearer in the past few years that certain subgroups of patients with PAH, particularly patients with scleroderma-related PAH (SSc-PAH), have a strikingly divergent response to therapy and overall worse outcome compared with patients with IPAH in spite of seemingly milder hemodynamic alterations [8–10]. While the reasons for these clinical differences remain unclear, there may be fundamental structural changes involving the pulmonary vasculature and the RV in patients with SSc-PAH [9,11], resulting in marked RV-pulmonary vascular dysfunction in this entity and poorer outcomes.

In addition, it has become evident that several issues have substantially limited progress in the diagnosis and management of SSc-PAH. First, currently available outcome measures, including the 6-min walk test (6MWT) and invasive or noninvasive cardiopulmonary hemodynamics, provide global assessments of function. They do not allow dissection or consideration of the components of the cardiovascular response, in particular RV function, proximal and distal vascular remodeling, and the interaction between the pulmonary vasculature and the RV, which may be particularly important in patients with SSc-PAH. Furthermore, while some progress has been made in understanding the genetics of IPAH with the discovery of specific mutations in the bone morphogenesis protein receptor 2 [12,13], little is known about genetic and/or phenotypic characteristics that might predict the development of PAH, RV-pulmonary vasculature dysfunction, response to therapy and survival in patients with SSc-PAH. Finally, delay in diagnosis and referral to specialized centers for treatment of PAH may be a contributing factor to poor prognosis in these patients. The goal of this review is to discuss specific features of SSc-PAH, currently available therapy for this entity and potential future therapeutic developments based on newly acquired knowledge of this disorder.

Systemic sclerosis

Systemic sclerosis is a heterogeneous disorder characterized by dysfunction of the endothelium, dysregulation of fibroblasts resulting in excessive production of collagen, and abnormalities of the immune system [14]. These processes lead to progressive fibrosis of the skin and internal organs, resulting in organ failure and death. Although the etiology of SSc is unknown, genetic and environmental factors are thought to contribute to host susceptibility [15]. SSc, whether presenting in the limited or diffuse form, is a systemic disease with the potential for multiple organ system involvement, including the gastrointestinal, cardiac, renal and pulmonary systems [16]. Pulmonary manifestations include PAH, interstitial fibrosis and increased susceptibility to lung neoplasms.

Estimates of incidence and prevalence of SSc have varied widely with the period of observation, disease definition and population studied [17]. Although the incidence seemed to be increasing over the period from 1940 to 1970, the rate of occurrence has stabilized since the widespread use of a standard classification system [18]. However, there continues to be marked geographic variation in the occurrence of the disease, supporting a role for environmental factors in disease pathogenesis. Prevalence of SSc ranges from 30 to 70 cases

per million in Europe and Japan [19–21], to approximately 240 cases per million in the USA [18]. Incidence varies similarly by geographic area, with the highest rates found in the USA (~19 persons per million per year) [17].

Prevalence of scleroderma-related PAH

Estimates of the prevalence of PAH in patients with SSc have varied widely based on the definition of pulmonary hypertension and the method of obtaining the measurements (i.e., echocardiography or cardiac catheterization). Using echocardiography as the diagnostic tool, prevalence of pulmonary hypertension in scleroderma ranges between 35 and 49% [22,23]. In a study of 709 consecutive patients who underwent echocardiography, the prevalence of pulmonary hypertension (defined as RV systolic pressure > 35 mm Hg) was 38% [24]. Similarly, using echocardiography as the principal mode of detection in patients with so-called limited SSc or the calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly and telangiectasias (CREST) syndrome, the prevalence of pulmonary hypertension, PAH is reported to be as high as 60% [10,23,25,26]. However, relying on cardiac catheterization for diagnosis, more recent studies have shown that the prevalence of pulmonary hypertension is indeed between 8 and 12% [27,28], a more conservative and accurate figure regarding this complication. In all patients with SSc, PAH significantly worsens survival and is, after interstitial lung disease, the leading cause of mortality in these patients [18,29,30]. With a conservative estimate of PAH prevalence of 10% among patients with SSc in the USA, the prevalence of SSc-PAH may be as high as 24 individuals per million, which indicates that SSc-PAH might be more common than other forms of PAH in the WHO group 1, including IPAH. Thus, with 1-year survival rates for SSc-PAH patients ranging from 50 to 87% [8–10, 27,29] (considerably lower than the 88% 1-year survival for IPAH patients [31]), the current onus for the PAH community is to develop improved therapies for these particular patients.

Clinical features

Risk factors for the development of PAH in SSc patients include late-onset disease [24], an isolated reduction in diffusing capacity for carbon monoxide (DLCO), a forced vital capacity (FVC)/DLCO ratio of less than 1.6 [32,33], or a combined decreased DLCO/alveolar volume with elevation of serum *N*-terminal pro-brain natriuretic peptide (*N*-Tpro-BNP) levels (Box 1) [34]. Typically, patients with SSc-PAH are predominantly women, have limited SSc, are older and have seemingly less severe hemodynamic impairment compared with IPAH patients [9]. Like in IPAH, clinical symptoms are nonspecific, including dyspnea and functional limitation, which may be more severe than in IPAH, due not only to older age but also to frequent involvement of the musculoskeletal system in these patients. SSc-PAH patients also tend to have other organ involvement, such as renal dysfunction and intrinsic heart disease. Indeed patients with SSc (even in the absence of PAH) tend to have depressed RV function [35,36] and left ventricle systolic, as well as diastolic, dysfunction [37]. Like IPAH patients, SSc-PAH patients have severe RV dysfunction at time of presentation but have more severely depressed RV contractility compared with IPAH patients [11]. In addition, SSc-PAH patients more commonly tend to have left ventricle diastolic dysfunction and a high prevalence of pericardial effusion (34% compared with 13% for IPAH) [9]. In both groups, pericardial effusion portends a particularly poor prognosis [9]. SSc-PAH patients also tend to have more-severe hormonal and metabolic dysfunction, such as high levels of *N*-Tpro-BNP [38] and hyponatremia [39]. Both *N*-Tpro-BNP and hyponatremia have been shown at baseline [38,39], and with serial changes (for *N*-Tpro-BNP) [38], to correlate with survival in PAH.

Detection of the disease

An algorithm for detection of PAH in patients with SSc may be helpful if based on a combination of symptoms and screening echocardiography (Figure 1). In a large French study,

patients with SSc with a tricuspid regurgitation velocity (TRV) jet by transthoracic echocardiography greater than 3 m/s, or between 2.5 and 3 m/s if accompanied by unexplained dyspnea, were systematically referred for right heart catheterization [28]. This approach allowed detection of incident cases of SSc-PAH with less severe disease (as judged using hemodynamic data) compared with patients with known disease. Therefore, unexplained dyspnea should prompt a search for PAH in these patients, in particular in the setting of a low single-breath DLCO or declining DLCO over time [33], echocardiographic findings suggestive of the disease (elevated TRV jet, dilated RV or dilated atrium), or elevated levels of *N*-Tpro-BNP, which can reflect cardiac dysfunction and have been found to predict the presence of SSc-PAH [38]. Systematic screening should allow for detection of early disease and prompt therapy, which may, theoretically, be beneficial from a prognostic standpoint [40].

Survival & outcome measures in PAH

Since the year 2000, over 1000 patients have been entered in multicenter, placebo-controlled trials of PAH therapy. These trials have used simple outcome measures to assess treatment efficacy, that is, essentially, the nonencouraged 6MWT and resting hemodynamics [41,42]. The 6MWT is a simple and noninvasive submaximal exercise test that correlates with cardiopulmonary performance [43] and has a strong independent association with mortality [31,43–45]. The changes in outcome measures in these trials were small but significant (e.g., mean increases in the walking distance ranging between 17 and 70 m and decreases in mean pulmonary arterial pressures of only a few mmHg [42,44]) but correlated, in some studies, with improved survival [44] and functional status [42,44]. This suggested that response to therapy was only partly related to resting hemodynamic measurements. However, a meta-analysis conducted by Macchia *et al.* on data from 16 randomized and fairly homogenous (in their inclusion of patients from group 1 of the WHO classification, with similar functional class [FC]) clinical trials of PAH therapy revealed that changes in 6MWT were not predictive of survival [46], therefore raising concerns about the use of 6MWT as a valid end point [47]. With the advent of more effective therapy, such as intravenous epoprostenol and endothelin receptor antagonists, placebo-controlled trials in PAH are less likely, and novel and more reliable outcome measures are needed to detect significant and predictive functional changes when comparing the effects of different drugs or combination therapy with standard PAH therapy. Recognizing the limitations of the currently employed outcome measures, a call for improved outcome measures, which would ideally be reproducible, more specific to cardiac or pulmonary vascular function, and predictive of survival, has been made [48,49].

Box 1

Risk factors for the development of pulmonary arterial hypertension in systemic sclerosis

• Limited systemic sclerosis	[33]
• Late age of onset	[24]
• Raynaud's phenomenon	[33]
• ↓ DLCO	[33,34]
• FVC/DLCO < 1.6	[33]
• ↑ <i>N</i> -Tpro-BNP serum level	[34]
• Antibodies (e.g., anti-U3 RNP)	[26]

DLCO: Diffusing capacity for carbon monoxide; FVC: Forced vital capacity; *N*-Tpro-BNP: *N*-terminal pro-brain natriuretic peptide; RNP: Ribonucleoprotein.

Therapy for scleroderma-related PAH

As discussed earlier, evidence of chronically impaired endothelial function [50–52], affecting vascular tone and remodeling, has been the basis for current PAH therapy. Vasodilator therapy using high-dose calcium channel blockers is an effective long-term therapy [53], but only for a minority of patients (e.g., <7% of IPAH patients [54]) who demonstrate acute vasodilation (e.g., to nitric oxide or adenosine) during hemodynamic testing, and an even smaller number of patients with SSc-PAH. Indeed, the vast majority of SSc-PAH patients fail to show a vasodilator response to acute testing [55]. Therefore, high-dose calcium channel therapy is not usually indicated for patients with SSc-PAH, although most patients often receive these drugs at low dosage, typically for the treatment of Raynaud's syndrome.

Anti-inflammatory drugs

It has been increasingly recognized that inflammation may play a significant role in various types of pulmonary hypertension [56], including IPAH and PAH associated with CTD and HIV infection. Interestingly, occasional patients with severe PAH associated with some forms of CTD (e.g., systemic lupus erythematosus, primary Sjögren syndrome and mixed CTD) have had dramatic improvement of their pulmonary vascular disease with corticosteroids and/or immunosuppressive therapy [57], emphasizing the relevance of inflammation in these subsets of patients. However, this type of dramatic response is not generally observed in patients with SSc-PAH whose disease is usually quite refractory to immunosuppressive drugs [57].

Prostaglandins

Prostacyclin (e.g., epoprostenol) has potent pulmonary vasodilator and also antiplatelet aggregating and antiproliferative properties [58], and has been proven to be effective in improving the exercise capacity, cardiopulmonary hemodynamics, New York Heart Association (NYHA) FC, symptoms and survival in patients with PAH when administered by continuous infusion [44,59,60]. Although there have been no randomized trials using this agent to assess the long-term effect on survival, analysis of cohorts of patients on continuous intravenous epoprostenol compared with historical control groups (a questionable comparison for many obvious reasons) demonstrated clear benefits in survival in patients with NYHA classes III and IV [31,45]. Initially proposed as a bridge to lung transplantation, intravenous epoprostenol is now considered first-line therapy in severe PAH (NYHA IV), and in some patients an alternative to lung transplantation [61]. Treprostinil, a prostacyclin analogue suitable for continuous subcutaneous administration, has been shown to have modest effects on symptoms and hemodynamics in PAH [62]. In a small study of 16 patients (among whom six had CTD-related PAH), recently US FDA-approved intravenous treprostinil was shown to improve 6MWD, FC, and hemodynamics after 12 weeks of therapy [63]. Although the safety profile of this drug is similar to intravenous epoprostenol, required maintenance doses are usually twice as high compared with epoprostenol. However, for patients with SSc-PAH, the lack of requirement for ice packing and less-frequent mixing of the drug offer significant advantages considering these patients' sensitivity to cold exposure. In summary, both epoprostenol and treprostinil are FDA-approved for PAH, but are cumbersome therapies requiring continuous parenteral administration with potential numerous adverse and severe side effects (e.g., infection and possibility of pump failure [64]), which make these drugs less than ideal.

In SSc-PAH, continuous intravenous epoprostenol improves exercise capacity and hemodynamics [65] compared with conventional therapy; however, there has been no demonstrable effect on survival. In addition, several reports of pulmonary edema in SSc-PAH patients treated with prostaglandin derivatives, both in acute and chronic settings, have raised the suspicion of increased prevalence of veno-occlusive disease in these patients [66–68], and

concern regarding the usefulness of these drugs for this entity. In addition, considering the frequent digital problems and disabilities that these patients often experience, this form of therapy can be quite challenging and may increase the already heavy burden of disease in these patients. Nevertheless, intravenous prostaglandin therapy remains a valuable therapeutic option for patients with SSc-PAH with NYHA class IV, and in class III patients who demonstrate no improvement on oral therapy.

Endothelin receptor antagonists

Randomized, placebo-controlled trials of 12–16 weeks' duration demonstrated a beneficial effect of bosentan therapy on FC, 6MWD, time to clinical worsening and hemodynamics in PAH [42,69]. In these studies, approximately a fifth of the population consisted of SSc-PAH patients while a large majority had a diagnosis of IPAH. A subgroup analysis, performed by Rubin *et al.*, reported a nonsignificant trend towards a positive treatment effect on 6MWD among the SSc-PAH patients treated with bosentan compared with placebo [42]. At most, bosentan therapy prevented deterioration in these patients (as assessed by an increase of 3 m in the 6MWD in the treated group compared with a decrease of 40 m in the placebo group). The reason for this less-than-optimal effect of therapy in patients with SSc-PAH is unclear, but may be related to the severity of PAH at time of presentation, as well as other factors, such as, hypothetically, more-severe RV and pulmonary vascular dysfunction, as compared with patients with other forms of PAH (e.g., IPAH).

In a recent analysis of patients with CTD-associated PAH (e.g., patients with lupus, overlap syndrome and other rheumatological disorders) included in randomized clinical trials of bosentan, there was a trend toward improvement in 6MWD and improved survival compared with historical cohorts [70]. Our experience suggests that long-term outcome of first-line bosentan monotherapy is inferior in SSc-PAH compared with IPAH patients, with no change in FC and worse survival in the former group [71].

In an effort to target the vasoconstrictive effects of endothelin while preserving its vasodilatory action, selective endothelin-A receptor antagonists have been developed. Sitaxsentan, which is only approved in Europe for treatment of PAH, improved exercise capacity (i.e., change in peak volume of oxygen [VO₂] at week 12, which was the main end point of the study) [72]. Elevation in liver enzymes were noted in 10% of patients at the higher dose tested (300 mg administered orally once daily). Patients with PAH associated with CTD represented 24% of the study group. A *post hoc* analysis of 42 patients (33 patients who received the drug and nine patients who received placebo) with CTD-PAH demonstrated improved exercise capacity, quality of life and hemodynamics with sitaxsentan, although elevated liver enzymes were reported in two patients [73]. A large placebo-controlled, randomized trial of ambrisentan, the only currently FDA-approved selective endothelin receptor antagonist, improved 6MWD in PAH patients at week 12 of treatment; however, the effect was larger in patients with IPAH compared with patients with CTD-PAH (range: 50–60 m vs 15–23 m, respectively) [74]. Ambrisentan is generally well tolerated, although peripheral edema (in up to 20% of patients [74]) and congestive heart failure have been reported.

Phosphodiesterase inhibitors

Sildenafil, a phosphodiesterase type V inhibitor that reduces the catabolism of cGMP, thereby enhancing the cellular effects mediated by nitric oxide, has become a widely used and highly efficacious therapy for PAH. A recent clinical trial showed that sildenafil therapy led to an improvement in the 6MWD in patients with IPAH and PAH related to CTD or repaired congenital heart disease (patients were predominantly FC II or III) at all three doses tested (20, 40 and 80 mg, administered three-times daily). Since there were no significant differences in clinical effects and time to clinical worsening at week 12 between the doses, the FDA

recommended a dose of 20 mg three-times daily. In a *post hoc* subgroup analysis of 84 patients with PAH related to CTD (45% of whom had SSc-PAH), data from the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study suggest that sildenafil at a dose of 20 mg improved exercise capacity (6MWD), hemodynamic measures and FC after 12 weeks of therapy [75]. However, for reasons that remain unclear (but partly related to the limitations of that study such as *post hoc* subgroup analysis), there was no effect for the dose of 80 mg three-times daily on hemodynamics in this subgroup of patients with CTD-related PAH. For this reason, and because of the potential of increased side effects (e.g., bleeding from arteriovenous malformations common in these patients) at high doses, at our center we have opted for sildenafil dosage of 20 mg three-times daily for our SSc-PAH patients as standard therapy. Higher doses are occasionally attempted in cases of limited response. At this time, due to its favorable safety profile, oral sildenafil is our drug of choice for first-line oral therapy for SSc-PAH patients with FC II or III. The impact of long-term sildenafil therapy on survival in patients with SSc-PAH remains to be determined. Finally, the results of tadalafil, another promising phosphodiesterase antagonist for PAH therapy that has the advantage of single daily dosage over sildenafil, have not yet been published.

Tyrosine kinase inhibitors

The finding that there is pathologically aberrant proliferation of endothelial and smooth muscle cells in PAH [6], as well as increased expression of secreted growth factors, such as VEGF and bFGF, has caused a shift in paradigm in treatment strategies for this disease. Some investigators have likened this condition to a neoplastic process reminiscent of advanced solid tumors [76]. As a result, antineoplastic drugs have been tested in experimental models [77, 78] and some occasional patient case reports [79–81]. Two strategies are currently tested for treatment of PAH: disruption of PDGF- and of VEGF-signaling pathways. STI-571/imatinib (Gleevec®/Glivec®), originally developed specifically to inhibit the Bcr-Abl kinase, is the prototypical PDGF receptor (PDGFR) signaling inhibitor currently under investigation [82]. This and sorafenib (Nexavar®), the second drug currently being tested in PAH, are FDA-approved for other conditions (e.g., gastrointestinal malignancies and renal and hepatocellular carcinomas) and their efficacy is attributed to their dual inhibition of VEGF- and PDGF-signaling pathways. Based on evidence that PDGF signaling is an important process in the pathophysiology of PAH [83], imatinib has been tested and shown to be effective in experimental models of PAH [77]. A Phase II multicenter trial to evaluate the safety, tolerability and efficacy of this drug in patients with PAH has been completed in the USA and Europe and the results are pending. The use of these drugs for scleroderma-related interstitial lung disease is also being investigated. Whether these new antineoplastic drugs with anti-tyrosine kinase activity will have a role in scleroderma (where there is evidence for both dysregulated proliferation and increased expression of growth factors such as VEGF [84]) or in IPAHA remains to be determined.

Combined therapy

It is now common practice in various pulmonary hypertension centers to add drugs when patients fail to improve on monotherapy. Adding inhaled iloprost to patients receiving bosentan has been shown to be beneficial in a small, randomized trial [85]. Combining inhaled iloprost with sildenafil is mechanistically appealing and anecdotally efficacious, as these drugs target separate, potentially synergistic, pathways [85,86]. Several multicenter trials are now exploring the efficacy of various combinations of two oral drugs or one oral and one inhaled drug. The recently published results of the Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil (PACES) trial demonstrate that adding sildenafil (at a dose of 80 mg three-times daily) to intravenous epoprostenol improves exercise capacity, hemodynamic measurements, time to clinical worsening and quality of life [87]. Approximately 21% of these patients had CTD, including 11% with SSc-PAH. Although no specific subgroup analysis is

provided, improvement apparently mainly occurred in patients with IPAH and was limited to patients who had relatively better exercise function at baseline. We have recently reported our experience of adding sildenafil to patients with IPAH or SSc-PAH after they failed initial monotherapy with bosentan [88]. While the combination improved the 6MWD and FC in IPAH patients, the outcome in patients with SSc-PAH was less favorable, but may have halted clinical deterioration. In addition, there were more side effects reported in the SSc-PAH compared with the IPAH patients, including hepatotoxicity that developed after addition of sildenafil to bosentan monotherapy [88]. Sildenafil and bosentan are substrates of the CYP 3A4 cytochrome, and combination therapy leads to significant increases in bosentan serum levels and significant decreases in sildenafil concentration (as bosentan induces CYP 3A4) [89]. The clinical significance of these findings is currently unclear, and these two drugs are often used in combination in clinical practice without obvious untoward effects.

Anticoagulation

The rationale for the use of anticoagulation in severe PAH is based on pathologic evidence of pulmonary thromboembolic arterial disease and thrombosis *in situ* in patients with IPAH [90], and two clinical studies (a retrospective analysis [91] and a small, nonrandomized prospective study [53]) demonstrating a significant beneficial effect of anticoagulation on survival in IPAH. In the former study, survival was significantly prolonged for patients who received long-term anticoagulation therapy, as compared with those who were not treated with warfarin [91]. In a study primarily aimed at assessing the effects of high-dose calcium channel blockers on IPAH, improved survival with oral anticoagulation was demonstrated *a posteriori*, irrespective of vasodilator use [53]. Based essentially on the findings of these two studies, anticoagulation is routinely recommended in the treatment of IPAH patients. The role of anticoagulation in other forms of PAH, in particular in SSc-PAH or other forms of CTD, is less clear. Theoretically, there is potential for increased bleeding in patients with CTD, particularly in those with SSc where gastrointestinal telangiectasias may be common. Our experience with anticoagulation in over 100 patients with SSc-PAH suggests that less than 50% of these patients remain on long-term anticoagulation therapy. The reason for discontinuing anticoagulation is often related to occult bleeding in the gastrointestinal tract from a source that is, in our experience, often difficult to diagnose.

Lung transplantation

Lung transplantation (LT) is typically offered as a last resort to patients with PAH who fail to respond to medical therapy. Although CTD is not an absolute contraindication to LT, patients with CTD often have associated morbidity and organ dysfunction other than the lung that place them at a specifically high risk for LT. The involvement of the esophagus with severe motility disorder and gastroesophageal reflux in patients with SSc is an example of specific risk that surgeons do not take lightly owing to the enhanced postoperative potential of aspiration and damage to the recipient lung. For these reasons, patients with SSc-PAH are often denied the LT option. However, if properly screened and approved for LT, patients with SSc experience similar rates of survival 2 years after the procedure compared with patients who receive LT for pulmonary fibrosis or IPAH [92].

Survival of patients with connective tissue disease & PAH

While there has been a recent significant increase in the number of drugs targeting specific pathways in PAH [7], survival of patients with CTD and PAH on modern therapy remains unacceptably low, despite recent claims of improvement trends in patients with SSc-PAH compared with similar historical controls [40]. The reason for a discrepancy in survival between IPAH patients and patients with CTD and PAH, particularly SSc-PAH, remains poorly understood and may involve complex pathogenic alterations affecting not only the proximal

and distal pulmonary vessels but also the heart (such as inflammatory myocarditis). Thus, a better understanding of the underlying pathophysiology of pulmonary vascular and cardiac remodeling, as well as RV-pulmonary vascular coupling in this disease, is needed for better targeted therapy. Whether specific anti-inflammatory agents or drugs targeting tyrosine kinase activity hold any promise of enhanced response is unclear at this time but needs further exploration.

Conclusion

SSc-PAH is a common cause of pulmonary hypertension but has significantly worse outcome compared with other diseases within group 1 of the WHO classification, such as IPAH. In addition, modern therapy for PAH appears to be of limited value in SSc-PAH. Similarly, currently available markers of disease severity or response to therapy in SSc-PAH are either limited or lacking. Therefore, there is an urgent need to identify potential genetic causes and novel physiologic and imaging biomarkers that will allow a better understanding of the underlying pathogenesis and serve as reliable tools for monitoring therapy in this devastating syndrome.

Expert commentary

Scleroderma-related PAH remains a syndrome that is difficult to treat with currently available medical therapy, for reasons that are poorly understood. Although classified within the group 1 (PAH) of the WHO classification, response to therapy is poor compared with other diseases within that group. In addition, considering the multisystem impact of SSc-PAH, currently used end points for judging the potential efficacy of drugs appear to be inadequate. A better understanding of the pathophysiology of the pulmonary vascular remodeling in this syndrome, and its impact on the heart (which may be equally affected in scleroderma) is greatly called for, and will hopefully provide clues to more effective therapy.

Five-year view

There will be hope for improvement in survival for patients with scleroderma-related PAH after a better understanding of the genetics of this disease and the factors (e.g., inflammatory processes) that govern the remodeling of the pulmonary vasculature and rapid failure of the right ventricle under increasing load. Based on these improvements, specifically targeted therapy, which may include anti-inflammatory and anti-proliferative drugs, will probably replace current vasodilator therapies.

Key issues

- Pulmonary hypertension is a common complication of systemic sclerosis and generally portends a very poor prognosis.
- Response to modern therapy for scleroderma-related pulmonary arterial hypertension (PAH) is poor compared with other PAH types.
- A poor prognosis in scleroderma-related PAH (SSc-PAH) may be related to the multisystemic nature of the disease and, particularly, involvement of the heart.
- Currently used end points to assess drug efficacy for PAH may be inadequate in SSc-PAH.
- A better understanding of right ventricle-pulmonary coupling in SSc-PAH might offer valuable insights in designing a more efficient therapy.

- Early detection of PAH and referral to pulmonary hypertension centers for treatment will theoretically improve prognosis and survival.
- A search for genetic factors and pathogenic mechanisms involved in scleroderma is warranted and will allow development of targeted therapy, such as anti-inflammatory and/or antiproliferative agents.

Acknowledgments

Financial & competing interests disclosure

Paul Hassoun's research is supported by NHLBI grant HL084946. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;115(5):343–349. [PubMed: 1863023]
2. Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet* 1998;352:719–725. [PubMed: 9729004]
3. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;107(2):216–223. [PubMed: 3605900]
4. Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004;43(12 Suppl):S5–S12.
5. Chin KM, Kim NH, Rubin LJ. The right ventricle in pulmonary hypertension. *Coron Artery Dis* 2005;16(1):13–18. [PubMed: 15654194]
6. Budhiraja R, Tuder RM, Hassoun PM. Endothelial dysfunction in pulmonary hypertension. *Circulation* 2004;109(2):159–165. [PubMed: 14734504]
7. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004;351(14):1425–1436. [PubMed: 15459304]
8. Kawut SM, Taichman DB, Archer-Chicko CL, Palevsky HI, Kimmel SE. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest* 2003;123(2):344–350. [PubMed: 12576350]
9. Fisher MR, Mathai SC, Champion HC, et al. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. *Arthritis Rheum* 2006;54(9):3043–3050. [PubMed: 16947776]
10. MacGregor AJ, Canavan R, Knight C, et al. Pulmonary hypertension in systemic sclerosis: risk factors for progression and consequences for survival. *Rheumatology (Oxford)* 2001;40(4):453–459. [PubMed: 11312386]
11. Overbeek MJ, Lankhaar JW, Westerhof N, et al. Right ventricular contractility in systemic sclerosis-associated and idiopathic pulmonary arterial hypertension. *Eur Respir J* 2008;31(6):1160–1166. [PubMed: 18216049]
12. Deng Z, Morse JH, Slager SL, et al. Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. *Am J Hum Genet* 2000;67(3):737–744. [PubMed: 10903931]
13. Lane KB, Machado RD, Pauculo MW, et al. Heterozygous germline mutations in BMPR2, encoding a TGF- β receptor, cause familial primary pulmonary hypertension. The International PPH Consortium. *Nat Genet* 2000;26(1):81–84. [PubMed: 10973254]
14. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. *Ann Intern Med* 2004;140(1):37–50. [PubMed: 14706971]
15. Tan FK. Systemic sclerosis: the susceptible host (genetics and environment). *Rheum Dis Clin North Am* 2003;29(2):211–237. [PubMed: 12841292]

16. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15(2):202–205. [PubMed: 3361530]
17. Mayes MD, Lacey JV Jr, Beebe-Dimmer J, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum* 2003;48(8):2246–2255. [PubMed: 12905479]
18. Mayes MD. Scleroderma epidemiology. *Rheum Dis Clin North Am* 2003;29(2):239–254. [PubMed: 12841293]
19. Silman A, Jannini S, Symmons D, Bacon P. An epidemiological study of scleroderma in the West Midlands. *Br J Rheumatol* 1988;27(4):286–290. [PubMed: 3261609]
20. Tamaki T, Mori S, Takehara K. Epidemiological study of patients with systemic sclerosis in Tokyo. *Arch Dermatol Res* 1991;283(6):366–371. [PubMed: 1796818]
21. Allcock RJ, Forrest I, Corris PA, Crook PR, Griffiths ID. A study of the prevalence of systemic sclerosis in northeast England. *Rheumatology (Oxford)* 2004;43(5):596–602. [PubMed: 14872101]
22. Murata I, Kihara H, Shinohara S, Ito K. Echocardiographic evaluation of pulmonary arterial hypertension in patients with progressive systemic sclerosis and related syndromes. *Jpn Circ J* 1992;56(10):983–991. [PubMed: 1433824]
23. Battle RW, Davitt MA, Cooper SM, et al. Prevalence of pulmonary hypertension in limited and diffuse scleroderma. *Chest* 1996;110(6):1515–1519. [PubMed: 8989070]
24. Schachna L, Wigley FM, Chang B, White B, Wise RA, Gelber AC. Age and risk of pulmonary arterial hypertension in scleroderma. *Chest* 2003;124(6):2098–2104. [PubMed: 14665486]
25. Stupi AM, Steen VD, Owens GR, Barnes EL, Rodnan GP, Medsger TA Jr. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum* 1986;29(4):515–524. [PubMed: 3707629]
26. Sacks DG, Okano Y, Steen VD, Curtiss E, Shapiro LS, Medsger TA Jr. Isolated pulmonary hypertension in systemic sclerosis with diffuse cutaneous involvement: association with serum anti-U3RNP antibody. *J Rheumatol* 1996;23(4):639–642. [PubMed: 8730118]
27. Mukerjee D, St George D, Coleiro B, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* 2003;62(11):1088–1093. [PubMed: 14583573]
28. Hachulla E, Gressin V, Guillemin L, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005;52(12):3792–3800. [PubMed: 16320330]
29. Koh ET, Lee P, Gladman DD, Abu-Shakra M. Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. *Br J Rheumatol* 1996;35(10):989–993. [PubMed: 8883438]
30. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis* 2007;66(7):940–944. [PubMed: 17329309]
31. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002;106(12):1477–1482. [PubMed: 12234951]
32. Chang B, Schachna L, White B, Wigley FM, Wise RA. Natural history of mild-moderate pulmonary hypertension and the risk factors for severe pulmonary hypertension in scleroderma. *J Rheumatol* 2006;33(2):269–274. [PubMed: 16465657]
33. Steen V, Medsger TA Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. *Arthritis Rheum* 2003;48(2):516–522. [PubMed: 12571862]
34. Allanore Y, Borderie D, Avouac J, et al. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. *Arthritis Rheum* 2008;58(1):284–291. [PubMed: 18163505]
35. Hsiao SH, Lee CY, Chang SM, Lin SK, Liu CP. Right heart function in scleroderma: insights from myocardial Doppler tissue imaging. *J Am Soc Echocardiogr* 2006;19(5):507–514. [PubMed: 16644433]
36. Lee CY, Chang SM, Hsiao SH, Tseng JC, Lin SK, Liu CP. Right heart function and scleroderma: insights from tricuspid annular plane systolic excursion. *Echocardiography* 2007;24(2):118–125. [PubMed: 17313542]

37. Meune C, Avouac J, Wahbi K, et al. Cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography during routine care: a controlled study of 100 consecutive patients. *Arthritis Rheum* 2008;58(6):1803–1809. [PubMed: 18512815]
38. Williams MH, Handler CE, Akram R, et al. Role of *N*-terminal brain natriuretic peptide (*N*-TproBNP) in scleroderma-associated pulmonary arterial hypertension. *Eur Heart J* 2006;27(12):1485–1494. [PubMed: 16682379]
39. Forfia PR, Mathai SC, Fisher MR, et al. Hyponatremia predicts right heart failure and poor survival in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2008;177(12):1364–1369. [PubMed: 18356560]
40. Williams MH, Das C, Handler CE, et al. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. *Heart* 2006;92(7):926–932. [PubMed: 16339813]
41. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med* 1994;121(6):409–415. [PubMed: 8053614]
42. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346(12):896–903. [PubMed: 11907289]
43. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000;161(2 Pt 1):487–492. [PubMed: 10673190]
44. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;334(5):296–302. [PubMed: 8532025]
45. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002;40(4):780–788. [PubMed: 12204511]
46. Macchia A, Marchioli R, Marfisi R, et al. A meta-analysis of trials of pulmonary hypertension: a clinical condition looking for drugs and research methodology. *Am Heart J* 2007;153(6):1037–1047. [PubMed: 17540207]
47. Rich S. The value of approved therapies for pulmonary arterial hypertension. *Am Heart J* 2007;153(6):889–890. [PubMed: 17540187]
48. Peacock A, Naeije R, Galie N, Reeves JT. End points in pulmonary arterial hypertension: the way forward. *Eur Respir J* 2004;23(6):947–953. [PubMed: 15219011]
49. Hoeper MM, Oudiz RJ, Peacock A, et al. End points and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. *J Am Coll Cardiol* 2004;43(12 Suppl):S48–S55.
50. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1995;333(4):214–221. [PubMed: 7540722]
51. Tuder RM, Cool CD, Geraci MW, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med* 1999;159(6):1925–1932. [PubMed: 10351941]
52. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993;328(24):1732–1739. [PubMed: 8497283]
53. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;327(2):76–81. [PubMed: 1603139]
54. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005;111(23):3105–3111. [PubMed: 15939821]
55. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006;173(9):1023–1030. [PubMed: 16456139]
56. Dorfmueller P, Perros F, Balabanian K, Humbert M. Inflammation in pulmonary arterial hypertension. *Eur Respir J* 2003;22(2):358–363. [PubMed: 12952274]
57. Sanchez O, Sitbon O, Jais X, Simonneau G, Humbert M. Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. *Chest* 2006;130(1):182–189. [PubMed: 16840400]
58. Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. *N Engl J Med* 1990;323(1):27–36. [PubMed: 2113184]

59. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med* 1998;338(5):273–277. [PubMed: 9445406]
60. Rubin LJ, Mendoza J, Hood M, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Ann Intern Med* 1990;112(7):485–491. [PubMed: 2107780]
61. Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997;336(2):111–117. [PubMed: 8988890]
62. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;165(6):800–804. [PubMed: 11897647]
63. Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12-week trial. *Chest* 2006;129(3):683–688. [PubMed: 16537868]
64. Galie N, Manes A, Branzi A. Emerging medical therapies for pulmonary arterial hypertension. *Prog Cardiovasc Dis* 2002;45(3):213–224. [PubMed: 12525997]
65. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000;132(6):425–434. [PubMed: 10733441]
66. Farber HW, Graven KK, Kokolski G, Korn JH. Pulmonary edema during acute infusion of epoprostenol in a patient with pulmonary hypertension and limited scleroderma. *J Rheumatol* 1999;26(5):1195–1196. [PubMed: 10332990]
67. Palmer SM, Robinson LJ, Wang A, Gossage JR, Bashore T, Tapson VF. Massive pulmonary edema and death after prostacyclin infusion in a patient with pulmonary veno-occlusive disease. *Chest* 1998;113(1):237–240. [PubMed: 9440597]
68. Dorfmueller P, Humbert M, Perros F, et al. Fibrous remodeling of the pulmonary venous system in pulmonary arterial hypertension associated with connective tissue diseases. *Hum Pathol* 2007;38(6):893–902. [PubMed: 17376507]
69. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358(9288):1119–1123. [PubMed: 11597664]
70. Denton CP, Humbert M, Rubin L, Black CM. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. *Ann Rheum Dis* 2006;65(10):1336–1340. [PubMed: 16793845]
71. Girgis R, Mathai SC, Krishnan JA, Wigley FM, Hassoun PM. Long-term outcome of bosentan treatment in primary pulmonary hypertension and pulmonary arterial hypertension associated with the scleroderma spectrum of diseases. *J Heart Lung Transplant* 2005;24(10):1626–1631. [PubMed: 16210140]
72. Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004;169(4):441–447. [PubMed: 14630619]
73. Girgis RE, Frost AE, Hill NS, et al. Selective endothelin A receptor antagonism with sitaxsentan for pulmonary arterial hypertension associated with connective tissue disease. *Ann Rheum Dis* 2007;66(11):1467–1472. [PubMed: 17472992]
74. Galie N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 2008;117(23):3010–3019. [PubMed: 18506008]
75. Badesch DB, Hill NS, Burgess G, et al. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. *J Rheumatol* 2007;34(12):2417–2422. [PubMed: 17985403]
76. Adnot S. Lessons learned from cancer may help in the treatment of pulmonary hypertension. *J Clin Invest* 2005;115(6):1461–1463. [PubMed: 15931382]
77. Schermuly RT, Dony E, Ghofrani HA, et al. Reversal of experimental pulmonary hypertension by PDGF inhibition. *J Clin Invest* 2005;115(10):2811–2821. [PubMed: 16200212]

78. Moreno-Vinasco L, Gomberg-Maitland M, Maitland ML, et al. Genomic assessment of a multikinase inhibitor, sorafenib, in a rodent model of pulmonary hypertension. *Physiol Genomics* 2008;33(2): 278–291. [PubMed: 18303084]
79. Ghofrani HA, Seeger W, Grimminger F. Imatinib for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2005;353(13):1412–1413. [PubMed: 16192491]
80. Patterson KC, Weissmann A, Ahmadi T, Farber HW. Imatinib mesylate in the treatment of refractory idiopathic pulmonary arterial hypertension. *Ann Intern Med* 2006;145(2):152–153. [PubMed: 16847299]
81. Souza R, Sitbon O, Parent F, Simonneau G, Humbert M. Long term imatinib treatment in pulmonary arterial hypertension. *Thorax* 2006;61(8):736. [PubMed: 16877696]
82. Carroll M, Ohno-Jones S, Tamura S, et al. CGP 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL, and TEL-PDGFR fusion proteins. *Blood* 1997;90(12): 4947–4952. [PubMed: 9389713]
83. Eddahibi S, Humbert M, Sediame S, et al. Imbalance between platelet vascular endothelial growth factor and platelet-derived growth factor in pulmonary hypertension. Effect of prostacyclin therapy. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1493–1499. [PubMed: 11029367]
84. Grigoryev DN, Mathai SC, Fisher MR, et al. Identification of candidate genes in scleroderma-related pulmonary arterial hypertension. *Transl Res* 2008;151(4):197–207. [PubMed: 18355767]
85. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006;174(11):1257–1263. [PubMed: 16946127]
86. Hoeper MM, Leuchte H, Halank M, et al. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2006;28(4):691–694. [PubMed: 17012628]
87. Simonneau G, Rubin LJ, Galie N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008;149(8):521–530. [PubMed: 18936500]
88. Mathai SC, Girgis RE, Fisher MR, et al. Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. *Eur Respir J* 2007;29(3):469–475. [PubMed: 17079256]
89. Hoeper MM, Faulenbach C, Golpon H, Winkler J, Welte T, Niedermeyer J. Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2004;24(6): 1007–1010. [PubMed: 15572546]
90. Pietra GG, Edwards WD, Kay JM, et al. Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. *Circulation* 1989;80(5):1198–1206. [PubMed: 2805258]
91. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984;70(4):580–587. [PubMed: 6148159]
92. Schachna L, Medsger TA Jr, Dauber JH, et al. Lung transplantation in scleroderma compared with idiopathic pulmonary fibrosis and idiopathic pulmonary arterial hypertension. *Arthritis Rheum* 2006;54(12):3954–3961. [PubMed: 17133609]

Figure 1. Algorithm for detection of pulmonary arterial hypertension in patients with systemic sclerosis

Proposed algorithm for performance of routine clinical tests in patients with systemic sclerosis, which may allow early detection of pulmonary arterial hypertension or other causes of cardiac dysfunction (e.g., left ventricular dysfunction). DLCO: Diffusing capacity for carbon monoxide; FVC: Forced vital capacity; N-Tpro-BNP: N-terminal pro-brain natriuretic peptide; PFT: Pulmonary function test; PH: Pulmonary hypertension; RHC: Right heart catheterization; RV: Right ventricle; TRV: Tricuspid regurgitation velocity.